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CNS DEPRESSANTS

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It is the purpose of this paper to review available information on central nervous system (CNS) depressants, including their prevalence, abuse potential, and treatment.

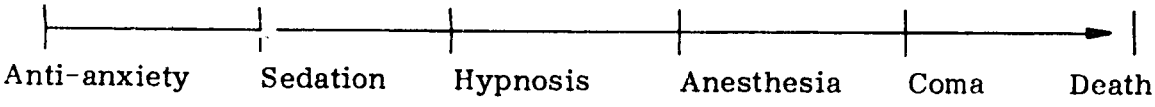
The following discussion of CNS depressants is limited to the barbiturates, the non-barbiturate sedative-hypnotics, and the anti-anxiety drugs, the minor tranquilizers. Alcohol, one of the most widely used CNS depressants in the United States, is excluded from this paper. The alcohol problem is of such proportion and unique nature that it requires independent attention. Also beyond the scope of this paper are the opiates, the anesthetic gases, the antihistamines, the belladonna alkaloids, and the reserpine, phenothiazine and butyrophenone groups of antipsychotic drugs, known as the major tranquilizers.

Central Nervous System Effects

The central nervous system consists of all the nerve cell bodies and fibers called neurones which compose the brain and spinal cord. The human brain alone contains approximately 12 billion neurones and the number of possible interconnections is so vast and complex that the physiology, biochemistry, pathology, and consequently the pharmacology of the CNS is not completely understood.

The CNS depressants affect the central nervous system in such a manner as to inhibit or impair the transmission of neurological signals. As a result, these drugs act to "depress" a wide range of physiological and cellular functions in many vital organ systems. The action of CNS depressants should be distinguished from the psychological state of "depression," which is a mood characterized by feelings of hopelessness, worthlessness, inferiority, and guilt.

While individual drugs differ in their potency and maximal effects, the CNS depressants produce effects along a continuum which defines deeper levels of unconsciousness.



Sedation - state of decreased responsiveness to stimuli without producing sleep.
Hypnosis - altered state of consciousness, sometimes resembling sleep.
Anesthesia - state of loss of sensation.
Coma - state of unconsciousness from which the patient cannot be aroused even by powerful stimulation.

Many of these drugs may produce either sedation or hypnosis depending on the dosage levels; hence the term, "sedative-hypnotic."

Barbiturates

The barbiturates refer to any of the derivatives of barbituric acid (malonylurea). More than 2,500 barbiturates have been synthesized and, although approximately fifty of these have been approved for clinical use, only about a dozen are widely used. However, these drugs are the most common and perhaps the most valuable CNS depressants utilized in medicine today.

The traditional method of classifying the barbiturates is based upon their relative duration of action. The "ultrashort-acting" barbiturates, which include sodium methohexital (Brevital), sodium thiamylal (Surital), and sodium thiopental (Pentothal), are employed primarily as intravenous anesthetics, often in conjunction with nitrous oxide or other inhalational agents. The "short- to intermediate-acting" barbiturates are used primarily as sedative-hypnotic agents and include amobarbital (Amytal), sodium butabarbital (Butisol), sodium pentobarbital (Nembutal), secobarbital (Seconal), and vinbarbital (Delvinal). Phenobarbital (Luminal), mephobarbital (Mebaral), and methabarbital (Gemonil) are "long-acting" barbiturates and are used as sedative-hypnotics and as agents in the emergency treatment of convulsions.

While it must be kept in mind that the action of these drugs upon the central nervous system depends on the particular barbiturate, the dosage, the route of administration, the state of the CNS at the time of administration, and the degree of tolerance, if any, that may exist, it is possible to present some general information about the pharmacology and effects of the barbiturates.

Although they may be injected, oral administration is the safest and most common method of introducing barbiturates into the body. The drugs are absorbed rapidly from the stomach and, since there exists no impenetrable barrier to the diffusion of barbiturates, they enter the bloodstream and tend to be distributed rather uniformly throughout the body. The further distribution and concentration of the barbiturates in various tissues and organs is largely dependent upon lipid solubility and protein binding. Thus fat depots and protein-rich organ tissues accumulate the highest concentrations of the barbiturates. There exist great variations among the different barbiturate compounds. The highly lipid-soluble and protein-bound drugs, such as thiopental, are absorbed more readily by the brain and other organs, and are resultingly of quicker onset and shorter duration of action.

Whereas peripheral structures will not be directly affected until significantly higher dose levels are attained, the central nervous system is exquisitely sensitive to the depressant effects of the barbiturates and will exhibit physiological responses at sedative-hypnotic dosages. The barbiturates produce a general reduction in CNS

activity at sedative doses leading to drowsiness and muscular incoordination. However, in some instances, certain individuals have experienced anxiety and excitement rather than sedation following the administration of low doses of barbiturates. In hyperkinetic children, for example, both barbiturates and amphetamines produce effects opposite to those found in the normal population. Thus, while barbiturates produce excitability in these children, amphetamines are used for purposes of calming the hyperactive child. The after-effects of barbiturate-induced sleep may include drowsiness, hangover, headache, overt excitement and decrements in motor performance, which may last for several hours.

While the ultra-short acting barbiturates are administered intravenously to induce anesthesia for surgery, they do not (nor do other barbiturates) relieve pain. In fact, in the presence of severe pain the barbiturates are often incapable of producing sedation or sleep. At small doses the barbiturates may cause hyper-algesia, an increase in the reaction to painful stimuli.

Although the barbiturates can exert a depressant effect on the respiratory, renal, hepatic, cardiovascular and other biological systems, these effects are not significant until doses well above therapeutic levels are reached. The toxic state produced by these drugs will be discussed later.

The psychological effects observed following the ingestion of the barbiturates are remarkably similar to those produced by alcohol. As with all psychoactive drugs, the set (i.e., the personality and emotional state of the user), and the setting (i.e., the environment in which the drug is taken), greatly affect the outcome of the drug experience. Therefore, while one individual may find a pleasant, serene and relaxed enjoyment, another individual may feel hostile and aggressive. While low doses produce variable effects, moderate doses commonly reduce reaction time, impair mental functioning and memory, and result in slurred speech, a loss of inhibitions, a reduction in emotional control, and other effects resembling alcohol intoxication.

Nonbarbiturates

There are a number of CNS depressants, other than the barbiturates, which are used therapeutically for sleep-induction. The nonbarbiturate sedative-hypnotics are of widely diverse chemical structures and pharmacological properties, and some of the more representative and popular agents will be considered here. Most of these drugs have not been studied as extensively as the barbiturates but generally have been found to share the same disadvantages despite the advertising claims of the producers of new nonbarbiturate sedative-hypnotics which appear on the market every year.

Chloral hydrate (Noctec, Somnos), synthesized in 1832 and the oldest of the non-barbiturate sedative-hypnotic group, declined in popularity following the introduction of the barbiturates. Similar in its action to the barbiturates, chloral hydrate may have one advantage in that at low hypnotic doses (0.5 and 1.0 grams) it does not appear to suppress the rapid-eye-movement (REM) phase of sleep. Unconsciousness may rapidly ensue when chloral hydrate is taken in combination with alcohol (Mickey Finn, knockout drops).

Bromide was introduced into medicine in 1857 as a treatment for epilepsy and was used extensively until it was replaced by more efficacious substances. It is currently found in several over-the-counter preparations including Bromo-Seltzer, Nervine, Sleep-Eze and Sominex. Bromide is excreted slowly from the kidney and, having a half-life in the blood of roughly twelve days, toxic levels may be reached if the drug is taken daily over a period of weeks. Chronic bromide intoxication (bromism) may be characterized by impaired memory, drowsiness, dizziness, irritability, dermatitis (skin rash), and gastrointestinal distress. Delirium, hallucinations, mania, or coma may be present in severe cases.

Ethchlorvynol (Placidyl), a tertiary acetylenic alcohol, is a sedative-hypnotic of rapid onset and short duration of action. Maximum drug levels in the blood are attained after 1 to 1½ hours following administration and is no longer detectable after 3 hours. Sedative doses are 100 to 200 milligrams (mg.) and the hypnotic dose is 500 mg.

The cyclic ether, paraldehyde, is usually given orally in doses of 4 to 8 milliliters (ml.) to induce sleep. It is currently used mainly in institutions. The drug is rapidly absorbed and peak brain levels are reached in ½ hour. A large fraction is excreted unchanged from the lungs with the remainder being largely metabolized in the liver. As with the barbiturates, significant effects upon respiratory and cardiovascular systems are not seen until therapeutic dose levels are surpassed. At high concentrations paraldehyde has been found to inhibit the release of acetylcholine from nerve endings which may lead to muscle weakness and fatigue.

Introduced into clinical medicine in the mid-1950's, the piperidinedione derivatives, glutethimide (Doriden) and methyprylon (Noludar), closely resemble the action of the barbiturates. Although initially purported to possess certain advantages over the barbiturates, glutethimide and methyprylon have been found to be quite similar to secobarbital in their duration of action and sedative-hypnotic effect. Glutethimide also exhibits anticholinergic activity and has been utilized in the prevention of motion sickness. Both drugs induce sleep rapidly and incidences of side effects are rare. The oral hypnotic dose of glutethimide is 500 mg. and for methyprylon, 200 to 400 mg.

Drugs that are fat-bound, such as Doriden, Quaalude, and Prolixin (a tranquilizer), have a particularly dangerous aspect in that they are stored in the body's fatty tissue and are difficult to expel from the system. Thus, a person may apparently

recover from the adverse effects of one of these drugs only to have the stored drug released into the system, causing further complications. Doriden is particularly toxic and a drug used in many successful suicides.

Methaqualone (Quaalude, Sopor) is one of the most potent members of the quinazolone series of nonbarbiturate sedative-hypnotic compounds. It is readily absorbed from the gastrointestinal tract and is distributed in body fat, the liver and brain tissue. Methaqualone appears to act centrally in the brain and, unlike the barbiturates, does not directly depress activity in the midbrain reticular system or medulla. The standard hypnotic dose of the drug is 150 to 300 mg. and it possesses a longer duration of action than either Tuinal (amobarbital/secobarbital combination) or chloral hydrate.

Methaqualone has been a popular drug among young people in America. As with many drugs obtained from illicit sources, methaqualone is often mixed with other substances before being sold. This complicates treatment of methaqualone poisoning, since medical workers are often unaware of the presence of other drugs in the patient's system.

Anti-Anxiety Drugs

The minor tranquilizers are agents primarily utilized to lessen the anxiety associated with neurotic disorders, transient situational disturbances, character disorders and psychosomatic disorders. They are ineffective in the treatment of the anxiety and agitation associated with psychoses and, as such, are distinguished from the major tranquilizers (e.g., chlorpromazine). The minor tranquilizers produce their anti-anxiety and sedative effects without usually exerting significant impact on other mental or physical functioning. However, they may produce drowsiness and impaired motor function at slightly higher doses or in individuals who are sensitive to their effects.

Following their introduction into clinical medicine in the 1950's, the minor tranquilizers supplanted the use of all other drugs as daytime sedatives. They may be considered in the following categories: the propyl alcohols and carbamate derivatives and the benzodiazepine derivatives.

The most typical and popular of the propyl alcohols and carbamate derivatives is meprobamate (Miltown, Equanil). It is readily absorbed from the gastrointestinal tract and reaches peak blood levels in 1 to 2 hours. The drug is nearly indistinguishable from the barbiturates in its pharmacological properties. Primarily of use as an anti-anxiety agent, meprobamate is also employed as an hypnotic at bedtime. It has only limited application in musculoskeletal disorders and is inferior to other drugs in the treatment of petit mal epilepsy. Meprobamate can actually aggravate some forms of seizures, such as grand mal epileptic seizures. Compounds related to meprobamate with similar pharmacology and therapeutic uses include:

tybamate (Solacen, Tybatran); phenaglycodol (Ultran); carisoprodol (Soma, Rela); and hydroxyphenamate (Listica).

The benzodiazepine derivatives--chlordiazepoxide (Librium), diazepam (Valium), oxazepam (Serax)--display a pharmacological picture not unlike that of meprobamate including sedation, skeletal muscle relaxation and somewhat greater anti-convulsant activity. The relative duration of action of chlordiazepoxide is longer than that of diazepam which in turn is longer than that of oxazepam. All three drugs are used in the treatment of anxiety. They have also been used in the treatment of alcoholism, hallucinogenic drug crises, and certain types of epilepsy. The benzodiazepine drugs as a rule are not considered to be highly toxic drugs. Although toxicity levels vary among the drugs discussed here, all three are somewhat more toxic than meprobamate.

A new benzodiazepine derivative, clorazepate dipotassium (Tranxene) has recently appeared on the market.

Tolerance to CNS Depressants

The CNS depressants have all been shown to be capable of producing both tolerance and, if used chronically, physical dependence. Several mechanisms are involved in the development of tolerance to these agents. The barbiturates, chloral hydrate, glutethimide, methyprylon, and meprobamate stimulate the production of metabolic enzymes in the liver which inactivate these drugs. Adaptation of nervous tissue to the presence of the CNS depressants also occurs. As the individual becomes experienced as to the effects produced by these drugs, a certain amount of psychological control can be exerted. Acquired tolerance disappears almost completely after one to two weeks of abstinence.

Due to the similarity in action of these substances, the use of one CNS depressant is often substituted for another. Thus, for example, if one develops a dependence on one CNS depressant, the physical or psychological demands associated with the dependence may be met by using another depressant drug; that is to say, a cross-dependence develops. In a similar manner, if tolerance has developed to the use of a barbiturate, resistance to the effects of the other CNS depressants (including alcohol) will be observed (i.e., cross-tolerance). Because of this cross-tolerance, withdrawal symptoms from dependence upon one CNS depressant may be prevented or diminished by administration of another. This property is exploited therapeutically in the management of CNS depressant or alcohol withdrawal as well as non-medically when supplies of the drug of preference are unavailable.

History of CNS Depressant Use

Anxiety and insomnia, two of the most common human afflictions, were treated during the 19th century with the opiates, with bromide salts, chloral hydrate

(introduced in 1869), paraldehyde (1882) and alcohol. Because the opiates were known to produce physical dependence, because the bromides carried the risk of chronic bromide poisoning, and chloral hydrate and paraldehyde (their potential for dependence unknown) had an objectionable taste and smell, alcohol became the prescribed depressant drug of choice. But the search for a better drug continued because "pledged teetotalers" refused to use alcohol, and many other patients either didn't like its taste and smell or tended to take more than prescribed.

In 1903 barbital (Veronal) was introduced and soon became very popular. The new chemical was accidentally discovered by two German scientists, von Mering and Fischer. Among the advantages of the new barbiturates was their lack of odor and taste, their form which allowed precise quantities to be prescribed and dispensed, and their apparent lack of major adverse side effects. By the 1930's an estimated billion grains were being taken in the U.S. alone.

Evidence increasingly accumulated during the 1930's and 1940's indicated that when misused, barbiturates--especially the short-acting types--posed many of the same problems as alcohol with regard to the dependency syndrome. But the parallel between the effects of these two CNS depressants was not confirmed until almost a half-century after the introduction of barbital.

The campaign against nonmedical use began with 1942 and 1945 articles in Hygeia (now Today's Health), an American Medical Association publication designed for the lay public. Other magazines followed suit including Collier's with a 1949 article called "Thrill Pills Can Ruin You." States began passing laws against nonprescription barbiturates, arrests made newspaper headlines, black market barbiturates became profitable, and "thrill pills" and "goofballs" became popularized. At first the illicit users were mostly adults, many of whom would never have otherwise taken a sedative or sleeping pill.

Because the barbiturates came under frequent attack, efforts were revived in the 1940's to find additional drugs to compete for the flourishing market for depressants. Glutethimide, ethchlorvynol, and methyprylon appeared on the market in 1954 and 1955. Their manufacturers urged physicians to prescribe them precisely because they were nonbarbiturates. However, it was found that the same potential for abuse existed with these drugs, as well as with a second class of drugs introduced in the mid-1950's, the minor tranquilizers.

Prevalence of CNS Depressant Usage

Various estimating techniques are used in determining the epidemiology of CNS depressant usage. These include surveys of subpopulations such as adults, students, and cross-sections of the general population; statistics on production and prescription of depressants; data on drug-related deaths and hospital admissions; and law enforcement statistics including figures for arrests and confiscations.

If all use of CNS depressants were legal, valid and reliable statistics on the number and types of users, trends in patterns of use and the various effects on users would be fairly easy to obtain, as it is for tobacco. Official data provide knowledge of widespread illicit use, but this information in turn is reason for a reluctant attitude toward further data. Agencies fail to employ precise and consistent categories in collecting and presenting data from year to year. Statistics are affected by alterations in the drug laws, changes in the practices of enforcement agencies, and changes in the characteristics of the drug users and the drug market. Discussions of prevalence, therefore, are based on available, rather than complete, data.

Studies of the late 1960's and early 1970's reveal widespread use of both sedative-hypnotics (barbiturate and nonbarbiturate) and tranquilizers, with the use of the latter being slightly more popular. Fort (1969) estimates the number of users of prescription CNS depressants at between 20 and 25 million. Approximately 300 tons of barbiturates alone are consumed in the U.S. annually.

In a survey of California adults (Manheimer et al., 1968), 30 percent had used either prescription or nonprescription sedative-hypnotics and tranquilizers at one time or another, and frequent use was reported by 7 percent for sedative-hypnotics, and 10 percent for tranquilizers. Among frequent users, the most significant subgroup variables are age, sex, and marital status. Sedative-hypnotic use increases with age and occurs most often among those 60 and over, while frequent use of tranquilizers is greater among those between 30 and 60. Almost twice as many women as men are frequent users (but in overall depressant usage this discrepancy is diminished because of the greater use of alcohol by men, and persons who are separated or divorced report frequent use more often than single or married persons. Studies of barbiturate use alone (Chambers et al., 1972) indicate that whites, persons from the middle socioeconomic classes, and persons with higher educations are more likely to be regular users of barbiturates.

CNS depressant use has become much more common among younger people in recent years. According to an extensive 1969 study of college students (Blum), 24 percent had used sedative-hypnotics and 19 percent had used tranquilizers, but among those who had used both types of drugs, tranquilizer use was greater at a rate of 4 to 1. Motivations cited by these students were relief of tension by both types of users, reduction of sexuality by sedative-hypnotic users and avoidance of panic by tranquilizer users.

Physicians, especially general practitioners, remain the major source of CNS depressants for all age groups, but among minors parents are a significant source as well. It is now common to find the use of depressants at the fourth and fifth grade level, and a May 1972 survey of Los Angeles City Schools shows barbiturates to be the number one school drug problem, ahead of both marihuana and alcohol (Busch).

There appears to be a decline, however, in the utilization of physicians to obtain prescriptions for CNS depressants. Within a cross-section surveyed (Mellinger et al., 1967-68), 27 percent of the prescription drugs (including stimulants) which were used were obtained illicitly. Nonmedical sources (including over-the-counter) were used more by those under 30 and by more men than women, but those drugs obtained medically were used on a more continuing basis. CNS depressants are widely used for emotional needs and according to Mellinger the growing tendency to avoid the physician-as-source indicates a discrepancy of attitudes between physicians and patients as to whether or not emotional distress can be considered disabling, i.e., is it "dys-ease" or disease?

Fort (1969) estimates that 500,000 of the millions of users of CNS depressants can be considered abusers, i.e., use that is nonspecific, excessive in amount or duration of time used, serving to obscure real causes while treating symptoms, or not being beneficial. An estimated 50 percent of all barbiturates manufactured are of the short-to-intermediate acting variety which are particularly subject to abuse.

By 1971 barbiturates had reportedly taken a dominant place in the use of drugs as intoxicants (Wesson et al.). Chronic intoxication is seen most often in the 30 to 50 year age range, while teenagers and young adults are more involved in patterns of episodic intoxication. Although oral use of CNS depressants greatly predominates, these authors also report the existence of "barb freaks," or intravenous barbiturate use among young adults "who have a strong commitment to the illegal drug culture...Barbiturates are injected primarily for the 'rush' effect... experienced immediately after injection."

Some 50 percent of all narcotic-dependent persons also abuse CNS depressants, with approximately 30 percent of them dependent on both narcotics and depressants (Chambers et al., 1972).

Simultaneous abuse of barbiturates and amphetamines is also common (Jaffe, 1970) and the combination is said to produce more elevation of mood than either drug-type alone. This combination occurs in at least two other known abuse patterns. One is an alternating cycle of sedation and stimulation: using stimulants to overcome a drowsy hangover, and by evening use of depressants to ward off insomnia. Barbiturates are also used by the "speed freak" to produce sleep after several days of continuous amphetamine injection.

The Drug Enforcement Administration, formerly known as the Bureau of Narcotics and Dangerous Drugs (BNDD), reported in 1971 that 17 percent of those arrested for serious crimes in six major U.S. cities were current barbiturate users. According to arrest figures from Los Angeles County (Busch, 1972), seizures of barbiturates rose 2,000 percent in the preceding 5 years, more than for any other drug, and the data also showed no community was exempt from the problem. Of all the traffic accidents involving drugged individuals between 1970 and 1972 in another southern California county, 40 percent involved secobarbital.

Secobarbital (reds, red devils, red birds) is the compound seized most frequently from the illicit traffic in CNS depressants, with phenobarbital (phennies) second, pentobarbital (yellow bullets, yellow jackets) third, and secobarbital/amobarbital combinations (rainbows, tooies, double trouble) fourth (BNDD, 1972). Secobarbital also accounts for a disproportionate number of toxicology cases.

Estimates of deaths per year attributed to prescription CNS depressants range as high as 10,000, and the most commonly used estimate of barbiturate-caused deaths is over 3,000 annually. Barbiturate overdose is currently one of the major methods of committing suicide and will probably remain so because of their easy availability. Blum (1969) reported that 70 percent of those students admitting to suicide attempts via ingestion were CNS depressant users.

A major danger associated with CNS depressant use is that combined use with alcohol potentiates the action of both. Accidental overdose can occur under these circumstances, as well as when sleeping pills are left by the bedside and an already sedated and confused person ingests a lethal dose. Prescription CNS depressants presently account for over 50 percent of all accidental drug poisonings, with non-barbiturate sedative-hypnotics being the major cause, barbiturates second, and tranquilizers third (Simmons, 1972).

The discreditation of the barbiturates had its most recent effect in the popularity of the nonbarbiturate sedative-hypnotic methaqualone. Originally introduced in 1951 as an anti-malarial agent, its greater usefulness as a sedative-hypnotic brought it to the United States, via England, in 1965 as a barbiturate substitute.

Manufacturers' claims--now discredited--that methaqualone was superior to other CNS depressants in the quantity and quality of sleep produced, encouraged widespread manufacture, prescription, and distribution of the drug. A marked increase in use had begun by 1969, and by 1972 private physicians, teachers, hospitals and clinics, "street people," drug manufacturers, and the BNDD all confirmed the sudden illicit use of "soapers" (Zito, 1972). This drug enjoys the highest popularity among white suburban teenagers, who sometimes reported it was more available than marihuana. Although the William H. Rorer Co., manufacturer of Quaalude, claimed to have put strict control on the drug, free advertising samples were widely distributed to physicians. Methaqualone was introduced as a prescription drug, but it was not included on the 1971 list of controlled substances, and in May of 1972 the BNDD reported more than 275 incidences of poisonings, overdoses and suicide attempts during the previous year, resulting in 16 deaths.

Abuse Potential and Effects of Abuse

It is perhaps not surprising that the CNS depressants, which produce psychological and physical effects nearly identical to those of alcohol should have gained widespread acceptance and desirability as substances for nonmedical use. Many individuals have been introduced to these drugs through physicians' prescriptions

for therapeutic reasons, while others obtained initial contact by illicit channels. The potential for abuse of the CNS depressants is quite high, especially if doses exceeding therapeutic levels are taken. The patterns of abuse, as with alcohol, are varied and may range from periodic episodes of gross intoxication (acute) in an effort to achieve a state of well-being to prolonged, compulsive, daily use (chronic). The chronic abuse of the CNS depressants is characterized by psychological dependence and, if it is not terminated, will eventually lead to physical dependence.

As was previously noted, the central nervous system is exquisitely sensitive to the effects of the CNS depressants at therapeutic doses and few, if any, effects are seen on other physiological functions. However, at higher doses or following prolonged abuse, a variety of effects are manifested, the symptoms of which are detailed here.

The symptoms of acute and chronic intoxication with CNS depressants resemble those of intoxication with alcohol and include general sluggishness, difficulty in thinking, slowness of comprehension, poor memory, faulty judgment, shortened attention span, emotional instability, and exaggeration of basic personality traits. Irritability, quarrelsomeness, and moroseness are common. There may be laughing or crying without provocation, untidiness in personal habits, hostile and paranoid ideas, and suicidal tendencies. Overt signs may include slurred speech, staggering gait, nystagmus (i.e., involuntary eye movements), and tremor of the hands.

Chronic intoxication with CNS depressants results in the development of tolerance in which there is a loss of sensitivity to the general effects of the drug unless larger doses are taken. However, while tolerance may develop to the sedative and intoxicating effects, the lethal dose level appears to be unaltered. Therefore, the chronic user is no less susceptible to fatal overdose than the neophyte drug taker. The development of tolerance is very gradual and is not as marked or rapid as with the opiates.

Following prolonged chronic intoxication of one or more months, physical dependence may occur. The abrupt cessation or marked decrease in drug intake will result in a characteristic abstinence syndrome, termed the general depressant withdrawal syndrome. The severity of the symptoms is determined in part by the dose level attained before drug use was discontinued, although the duration of use may also play a significant role. The general depressant withdrawal syndrome may initially be evidenced by a reduction in intoxication and an apparent improvement in condition, but within 24 hours minor withdrawal phenomena are observable. These can include anxiety, apprehension, agitation, anorexia (i.e., loss of appetite), nausea, vomiting, excessive sweating, tachycardia (i.e., increased heart rate), hyperactive reflexes, insomnia, abdominal cramps, tremulousness, and muscle twitches. Orthostatic hypotension is characteristic and the individual may faint upon standing or sitting up suddenly. The symptoms usually peak during the second and

third days of abstinence from the short-acting barbiturates and meprobamate; however, peak effects may not be reached until the 7th or 8th days with the long-acting barbiturates and chlordiazepoxide. It is during this peak period that the major withdrawal phenomena, if they are to develop, usually emerge. Generalized convulsions can occur marked by seizures indistinguishable from those seen in grand mal epilepsy. The number of seizures varies from a single one to status epilepticus (i.e., continuous seizures). More than half of those individuals experiencing convulsions go on to develop delirium. Mild delirium may be characterized by mounting anxiety leading to visual hallucinations. As the delirium becomes more severe, sensory clouding and disorientation result in a psychotic state identical to the delirium tremens (D.T.'s) of the alcohol withdrawal syndrome. Agitation and elevated body temperature can lead to exhaustion and cardiovascular collapse which has resulted in death.

It should be emphasized that the full range of withdrawal effects only appears subsequent to heavy chronic use. Regular use of ordinary therapeutic doses does not usually cause significant tolerance nor physical dependence.

Overdose and Emergency Treatment

The lethal dose of the barbiturates and other CNS depressants cannot be ascertained with any accuracy. However, a general rule of thumb is that if more than ten times the full hypnotic dose of a drug is ingested at once, severe poisoning is likely to result. Many factors including potency, route of administration, and the biochemical composition of the individual affect the actual dosage at which death will occur. One dangerous aspect of CNS depressant abuse is the synergistic effect these drugs possess when taken in combination with one another or with alcohol. Relatively safe amounts of CNS depressants are potentiated to produce effects far greater than expected. These combinations are often lethal.

The toxic or poisoned state induced by barbiturate overdose is characterized by coma, a general shock syndrome (e.g., weak rapid pulse, low blood pressure, and cold sweaty skin) and may result in death due to respiratory arrest, cardiovascular collapse or kidney failure. Because the overdose of nonbarbiturate depressants presents a similar syndrome, the drug (or drugs) involved cannot be readily identified by physical examination. The presence of tablets or capsules, empty prescription vials, or friends of the victim may provide helpful clues. Although an accurate determination may be made by various laboratory methods, the overdose crisis situation requires immediate medical attention. For this reason, it is generally advisable to treat symptoms as they appear.

The comatose individual will display a level of reflex activity correlating to the intensity of central nervous system depression. The pupils may be pinpointed (maximally dilated in the case of glutethimide) but reactive to light. However, late in the course of CNS depressant poisoning the pupils may show paralytic

dilatation. Respiration may be either slow, or rapid and shallow, perhaps resulting in hypoxia (i.e., lack of oxygen) and respiratory acidosis. Respiratory complications including pulmonary edema and bronchial pneumonia are not uncommon. The ratio of cardiovascular to respiratory depression may be higher with non-barbiturate sedative-hypnotic overdose.

While debate continues as to the most efficacious treatment technique for CNS depressant overdose, certain lifesaving procedures are basic to all of them. Emergency management is directed primarily toward maintenance of vital cardiopulmonary functions. The establishment of an unobstructed airway is critical and, if respiration is depressed and oxygenation is inadequate, mechanical ventilation and administration of oxygen is initiated. To prevent death from circulatory collapse, transfusion of whole blood, plasma, or plasma expanders is begun, thereby elevating the blood pressure. Vasopressor drugs may be added to these fluids if shock symptoms persist, although it has been recommended that in the case of barbiturate poisoning this action not be taken. In these cases, the volume of infusion fluid can be increased in an effort to reduce shock. Once cardiopulmonary stability is achieved, additional treatment procedures are undertaken.

If there is evidence that the drug was ingested within a period of 4 to 12 hours before hospital admission, gastric lavage (i.e., the emptying of stomach contents) may be attempted to prevent further drug absorption. However, it has been found that very little drug is effectively removed. Although hemodialysis and renal dialysis are efficient methods for eliminating the presence of drugs in the body, they are of questionable lifesaving value except in the occurrence of renal failure. Hemodialysis is more effective in removing long-acting than short-acting compounds.

The role of various pharmacological agents in the treatment of CNS depressant overdose is particularly controversial. Some clinicians espouse the use of stimulants or analeptics (e.g., methylphenidate, pentylenetetrazol, nikethamide, caffeine) to reverse CNS depression, or vasopressors to elevate blood pressure, or diuretics to promote urinary excretion. Others, however, contend the presence of these substances may mask symptoms and place additional stress on an already taxed physiological system. Current treatment practices reflect the latter point of view.

Treatment of Chronic Abuse

The above discussion dealt with the essential emergency lifesaving procedures in a CNS depressant overdose. The concern in such situations centers on helping the patient through the immediate crisis brought about by overdose. Another dimension to treatment of CNS depressant abuse involves the treatment of the chronic abuser. In cases of chronic dependence on depressants, the individual must first undergo withdrawal.

Once an individual has been diagnosed as physically dependent on CNS depressants, the most immediate concern becomes the management of withdrawal. The procedure for withdrawal is analogous to that for withdrawal from opiates. After a determination has been made as to the amount of drug the person has been taking, gradual withdrawal is begun. Pentobarbital, a short-acting barbiturate, and phenobarbital, a long-acting one, are two of the more commonly used withdrawal agents. The drug on which the patient is dependent can also be used. The process involves gradually decreasing the dosage level until the individual finally no longer needs the drug to ward off withdrawal symptoms. If withdrawal symptoms appear, further decreases in the dosage level should be halted and the dosage maintained at that level until the symptoms disappear. The withdrawal process usually requires 2 to 3 weeks.

There are clear similarities between withdrawal from barbiturate and nonbarbiturate sedative-hypnotic drugs and, hence, the term "general depressant withdrawal syndrome" has been used in referring to withdrawal symptoms. Withdrawal after chronic abuse of depressant drugs can be extremely hazardous, depending on the rate of excretion of the drug. Abrupt withdrawal can cause severe convulsions, anxiety, hallucinations, disorientation, delirium, coma or death. When the patient enters the delirium phase, even administration of large dosages of barbiturates often fails to provide immediate relief. During the delirium, the patient may experience exhaustion and cardiovascular collapse. Because of these reactions, abrupt withdrawal (or "cold turkey") from both barbiturates and nonbarbiturate depressant drugs is to be guarded against.

Because of the life-threatening complications that can arise during the withdrawal phase, it is generally agreed that close supervision is needed, preferably on an inpatient basis. Although it is probably easier to maintain the necessary control in a hospital setting, outpatient withdrawal is possible and probably useful in reaching people who otherwise would not receive treatment. Gay, Smith, et al. (1971) describe such an outpatient program in which they used outreach workers to maintain daily contact with people in treatment in order to achieve necessary supervision. Their clients consisted of people who refused to submit to conventional hospitalization.

Dependence on CNS depressants, like other forms of drug dependence, is usually a chronic relapsing disorder. Many abusers follow a pattern of withdrawal followed by reversion to dependence. This situation often implies some form of underlying psychopathology, a problem more difficult to resolve than physical withdrawal.

Continuing treatment of the attendant psychological problems of the individual is essential. Individual supportive counseling is important, since a major problem involved is the inability of the individual to cope with stressful situations. Continued contact with the patient over a prolonged period of time will usually be required. In some cases there is a need for counseling or therapy for one or more members of the patient's family. In other cases, supportive therapy for the patient over a long period of time may be necessary.

Specialized treatment programs for CNS depressant abusers are, unfortunately, rare. Treatment is usually arranged on an individual case basis, taking into consideration the pattern of the abuse cycle and the particular needs of each patient.

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